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ESTIMATING EXPOSURE RESPONSE FUNCTIONS USING AMBIENT POLLUTION CONCENTRATIONS

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This paper presents an approach to estimating the health effects of an environmental hazard. The approach is general in nature, but is applied here to the case of air pollution. It uses a computer model involving ambient pollution and temperature input, to simulate the exposures experienced by individuals in an urban area, whilst incorporating the mechanisms that determine exposures. The output from the model comprises a set of daily exposures for a sample of individuals from the population of interest. These daily exposures are approximated by parametric distributions, so that the predictive exposure distribution of a randomly selected individual can be generated. These distributions are then incorporated into a hierarchical Bayesian framework (with inference using Markov Chain Monte Carlo simulation) in order to examine the relationship between short-term changes in exposures and health outcomes, whilst making allowance for long-term trends, seasonality, the effect of potential confounders and the possibility of ecological bias.

The paper applies this approach to particulate pollution (PM_{10}) and respiratory mortality counts for seniors in greater London ($\geq$65 years) during 1997. Within this substantive epidemiological study, the effects on health of ambient concentrations and (estimated) personal exposures are compared. The proposed model incorporates within day (or between individual) variability in personal exposures, which is compared to the more traditional approach of assuming a single pollution level applies to the entire population for each day. Effects were estimated using single lags and distributed lag models, with the highest relative risk, RR=1.02 (1.01-1.04), being associated with a lag of two days ambient concentrations of PM_{10}. Individual exposures to PM_{10} for this group (seniors) were lower than the measured ambient concentrations with the corresponding risk, RR=1.05 (1.01-1.09), being higher than would be suggested by the traditional approach using ambient concentrations.

Keywords: environmental epidemiology, air pollution, personal exposure simulator, Bayesian hierarchical models.

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1. Introduction. This paper addresses the differences between estimated associations observed in air pollution and human health studies, the nature and magnitude of which will depend fundamentally on the nature of the study. Concentration response functions (CRFs) are estimated primarily through epidemiological studies, by relating changes in ambient concentrations of pollution to a specified health outcome such as mortality (see Daniels et al. (2004) for example). In contrast exposure response functions (ERFs) have been estimated through exposure chamber studies, where the physiological reactions of healthy subjects are assessed at safe levels of the pollutant (see Ozone (2006) for example). However ERFs cannot be ethically established in this way for the most susceptible populations such as the very old and very young who are thought to be most adversely effected by pollution exposure. This paper presents a method for estimating the ERF based on ambient concentration measures.

We specifically consider the case of particulate air pollution, which has attained great importance in both the health and regulatory contexts. For example they are listed in the USA as one of the so-called criteria pollutants that must be periodically reviewed. Such a review by the US Environmental Protection Agency led to a 2006 revision of the US air quality standards (PM (2004)), which require that in US urban areas daily ambient concentrations of PM_{10} (particles no larger than 10 microns in diameter) do not exceed 150 $\mu g/m^3$ 'more than once a year on average over three years'. Concern for human health is a driving force behind these standards, as the US Clean Air Act of 1970 states they must be set and periodically reviewed to protect human health without consideration of cost while allowing for a margin of error.

In this paper we develop a model that estimates the ERF by relating personal exposures to daily health counts (aggregated over the entire population), and follows on from work by Holloman et al. (2004) and Shaddick et al. (2005). In particular we investigate the potential of using the pCNEM exposure simulator (Zidek et al. (2005)) to generate personal exposures, and compare the resulting associations with the CRFs estimated using routinely collected ambient concentrations. A case study is presented, in which relationships between (daily) respiratory mortality and both ambient concentrations (CRF) and individual (simulated) exposures (ERF) of particulate matter (PM_{10}) are examined, for seniors ($\geq$ 65 years) in Greater London (for 1997). Throughout we adopt a Bayesian approach to modelling, with inference using Markov Chain Monte Carlo simulation. The remainder of

the paper is organised as follows. Section 2 provides the background and motivation for this work, while section 3 describes the proposed model and section 4 presents the case study of data from Greater London. Section 5 provides a concluding discussion.

2. Background. The majority of studies relating air pollution with detrimental effects on health have focused on short-term relationships, using daily values of aggregate level (ecological) data from a fixed geographical region, such as a city. Such relationships are typically estimated by regressing daily mortality counts $\mathbf{y} = (y_1, \ldots, y_n)_{n\times 1}$ against air pollution concentrations and a vector of q covariates, $Z = (\mathbf{z}_1^{\mathrm{T}}, \ldots, \mathbf{z}_n^{\mathrm{T}})_{n\times q}^{\mathrm{T}}$. These covariates typically include meteorological conditions such as temperature together with smooth functions of calendar time, which model unmeasured risk factors that induce long-term trends, seasonal variation, over-dispersion and temporal correlation into the mortality data. In general, only ambient pollution concentrations, x_{jt}^A, measured by a network of k fixed site monitors located across the study region are available. A daily average $x_t^A = (1/k)\sum_{j=1}^k x_{jt}^A$ is typically calculated across these k spatial observations, which are assumed to represent population exposure. These ambient measures are related to the mortality counts using Poisson linear or additive models. A Bayesian implementation of the former is given by

$$\begin{aligned} y_t | x_{t-l}^A, \beta &\sim \text{Poisson}(\mu_t) \quad \text{for } t = 1, \ldots, n, \\ \ln(\mu_t) &= x_{t-l}^A \gamma + \mathbf{z}_t^{\mathrm{T}} \boldsymbol{\alpha}, \\ \boldsymbol{\beta} = (\gamma, \boldsymbol{\alpha}) &\sim \mathrm{N}(\boldsymbol{\mu}_\beta, \Sigma_\beta), \end{aligned} \tag{2.1}$$

where the Gaussian prior for $\boldsymbol{\beta}$ is typically vague. In this model the association between ambient pollution concentrations (at lag l) and mortality is represented by γ, and is of interest for regulatory purposes primarily because it is only ambient pollution concentrations that are routinely measured. However personal exposures are based on indoor as well as outdoor sources, and are likely to be different from ambient concentrations (see for example Dockery and Spengler (1981) and Lioy et al. (1990)) because the population spend a large proportion of their time indoors. Therefore to obtain more conclusive evidence of the human health impact of air pollution via an ERF, exposures actually experienced by individuals as well as any subsequent health events are required. Ideally, these would be obtained by individual level studies conducted under strict conditions, such as in randomised controlled trials, but issues of cost and adequate confounder control make them relatively rare (a few examples are given by Neas et al. (1999),

Yu et al. (2000) and Hoek et al. (2002)).

An alternative approach is to obtain only individual level pollution exposures, which can be related to routinely available (aggregated) health and confounder data. However such exposures are still prohibitively expensive to obtain for a large sample of the population, and consequently only a small amount of personal exposure data has been collected (see for example Lioy et al. (1990) and Ozkaynak et al. (1996)). As a result few studies have estimated the association between personal exposures and mortality, with one of the first being that of Dominici and Zeger (2000) who analyse data from Baltimore. However pollution exposures were not available and instead five external data sets were used to estimate a linear relationship between ambient concentrations and average exposures. The samples of personal exposures were small, which may lead to problems when assuming they represent overall population exposure.

A recent innovation is to generate simulated exposures using models such as SHEDS-PM (Burke et al. (2001)), APEX (Richmond et al. (2001)) and pCNEM (Zidek et al. (2005)), which have played an important role in formulating air quality criteria resulting in two important applications. The first and most widely used is to evaluate abatement strategies (e.g. regulations and mandatory surveillance), by running the model before and after hypothetical changes in policy (see Zidek et al. (2007)). The Environmental Protection Agency in the US have used such models to estimate carbon monoxide and ozone exposures (pNEM, a fore-runner to pCNEM Law et al. (1997)), while particulate matter has been modelled using SHEDS-PM. In addition the latest ozone criterion document (Ozone (2006)) made use of the APEX model, while Zidek et al. (2007) used pCNEM to forecast personal exposures of PM_{10} after a theoretical 'roll-back' programme. Although they differ in certain often fundamental respects, all of the simulators have important conceptual elements in common. Namely, they estimate the cumulative exposure experienced by individuals as they pass through different micro-environments, such as a car, house, street, which is calculated from the different pollution levels in each of these environments. The second application that is proposed in this paper has attracted far less attention, and uses exposure simulators to generate more accurate estimates of population exposures. Holloman et al. (2004) related simulated individual exposures to mortality data from North Carolina, using a deterministic simplification of the SHEDS-PM simulator (Burke et al. (2001)), an approach also used more recently by Reich et al. (2008). In a forerunner to this work, Shaddick et al.

(2005) related simulated daily exposures to mortality counts in London, observing an increased relative risk compared with ambient concentrations, but accompanied by a widening of the 95% credible interval.

Although the studies of Dominici and Zeger (2000) and Holloman et al. (2004) have related individual exposures to ecological mortality counts, the models used have a number of limitations. Primarily they summarise daily exposure distributions by a simple average while not allowing for the possibility of ecological bias (Wakefield and Salway (2001)), which may arise when variation in the exposures is ignored. When extending this simple average to allow for exposure variability both papers make a Gaussian assumption, which is likely to be inappropriate for non-negative environmental exposures of this type (see Ott (1990)).

3. Statistical modelling. Here we propose a two stage modelling strategy for generating and relating personal exposures to mortality, that differs from the 'all at once' approach adopted by Holloman et al. (2004). In the first stage, posterior exposure distributions for the population of interest are generated by pCNEM, a complex stochastic model, which is computationally expensive compared to the deterministic approach used by Holloman et al. (2004). The output from this first stage is a set of simulated personal exposures for each day of the study, which provide an approximation to the true distribution of exposures. If time activities were available for the entire population of interest and if it were possible to perform an infinite number of replicate runs of the exposure simulator then the exact distribution could be obtained. In the second stage, a Bayesian health model relates this exposure information to the aggregated health counts. For each day, the samples are used to inform the parametric distribution assumed for the exposures, the moments of which are treated as unknown parameters within the MCMC simulation. An alternative would be a fully Bayesian approach that integrates the exposure generation with the health model, thus allowing the uncertainty in the exposure distribution to be directly propagated through the model. However due to the complexities of the stochastic exposure generation, it would be computationally infeasible to perform the exposure stage within each iteration of a fully Bayesian model. In the following description, the first sub-section describes the pCNEM simulator, while the second proposes a model to relate these exposures to aggregated mortality counts.

3.1. *Stage 1: Estimating average population exposure.* The pCNEM simulator is described in detail in Zidek et al. (2005) and Zidek et al. (2007). Described simply, it generates a sequence of pollutant concentrations to which

a randomly selected individual is exposed over time. This sequence is termed the *personal exposure sequence*. The generation is a fairly complex stochastic process that follows the randomly selected individual in their activities over the period of the simulation. The individual is thought of as visiting one *microenvironment* (ME) after another as activities change through time. MEs are classified as being either 'open' or 'closed', with the former containing MEs whose concentrations can be well predicted by outdoor ambient concentrations and whose concentrations are estimated by regression models, incorporating the possibility of uncertainty in the coefficients. Closed MEs are more challenging in terms of data requirements since their concentrations are modelled with a mass balance equation (see Law et al. (1997) and Zidek et al. (2005)), but again the coefficients are allowed to exhibit uncertainty by using prior distributions. The interaction between environment and human behaviour is represented by a catalogue of behaviour patterns obtained from population surveys (e.g. National Human Activity Pattern Survey (NHAPS), a 24 hour recall survey Robinson and Thomas (1991). Behaviour conditional on individual and environmental stratification factors is simulated by sampling from appropriate subsections of the catalogue. It is assumed that the behaviour patterns in NHAPS will reflect a whole variety of both measured factors that determine behaviour, such as temperature, and also unmeasured ones, such as possible disease status. If it was thought that exposures were likely to be dependent on the presence of certain diseases, then more detailed time activities would be required for that particular group, but such data are not generally available.

The simulator has two major tasks; (i) to create estimates of the levels of pollution in each microenvironment over time and (ii) to generate an activity sequence for a randomly selected individual. The individual's cumulative level of exposure is then calculated by tracking them through their different activity levels within the microenvironments. The result is a sample of exposures for each day which represent the posterior distribution. Details on the data required to run the pCNEM simulator and how it can be accessed can be found in the supplementary material at *http://www.imstat.org/aoas/* and further details of the sampling of behaviour patterns and of the different modelling techniques used for estimating exposures in open and closed MEs can be found in Zidek et al. (2007).

3.2. *Stage 2: Estimating the effects of exposure to health.* We propose a model that extends the standard approach of representing daily pollu-

tion concentrations by a single value (for example the mean). Instead we assign a probability distribution to the daily exposures, which allows for the possibility of ecological bias. Comprehensive reviews of the relationship between aggregate and individual models as well as ecological bias are given by Richardson et al. (1987) and Wakefield and Salway (2001). For clarity, we present the remainder of this explanation with lag, $l = 0$. Assuming the standard log-linear model as in (2.1), then ecological bias can be modelled by considering the alternative mean function,

$$\begin{aligned} \mu_t &= \mathbb{E}_{X_t}[\exp\{\mathbf{z}_t^{\mathrm{T}}\boldsymbol{\alpha} + g(\gamma X_t)\}], \\ &= \exp(\mathbf{z}_t^{\mathrm{T}}\boldsymbol{\alpha})\mathbb{E}_{X_t}[\exp(g(\gamma X_t))], \end{aligned} \tag{3.1}$$

where X_t comes from the distribution of population exposure $f(x_t|\boldsymbol{\lambda})$ (Richardson et al. (1987)). The exposure response function is represented by g, and if we assume the common simplification $g(x) = x$, then the mean function equals

$$\begin{aligned} \mu_t &= \exp(\mathbf{z}_t^{\mathrm{T}}\boldsymbol{\alpha})\mathbb{E}_{X_t}[\exp(\gamma X_t)], \\ &\approx \exp(\mathbf{z}_t^{\mathrm{T}}\boldsymbol{\alpha})\exp(\gamma\lambda_t) \end{aligned} \tag{3.2}$$

with the second line arising when making the additional simplification that X_t can be represented by a single value, λ_t, such as the daily mean. In such cases, the variability in exposures is not acknowledged and thus there may be ecological bias. Richardson et al. (1987) and Salway and Wakefield (2008) model ecological bias parametrically in this context by incorporating higher order moments (for example the variance) of the exposure distribution $f(x_t|\boldsymbol{\lambda})$ in the linear predictor, in addition to the mean. If X_t is normally distributed, $X_t \sim N(\lambda_t^{(1)}, \lambda_t^{(2)})$, then the effects of exposure variability and ecological bias can be modelled exactly by adopting the mean function

$$\mu_t = \exp(\mathbf{z}_t^{\mathrm{T}}\boldsymbol{\alpha})\exp(\gamma\lambda_t^{(1)} + \gamma^2\lambda_t^{(2)}/2). \tag{3.3}$$

If the daily exposures do not follow a normal distribution equation (3.3) will be a second order approximation to the true model, which is likely to be adequate provided the distribution of X_t is not heavily skewed. Ott (1990) has shown that a log-normal distribution is appropriate for modelling exposures to pollution, because in addition to the desirable properties of right-skew and non-negativity, there is justification in terms of the physical explanation of

atmospheric chemistry. However, under the log-normal assumption ecological bias cannot be modelled in this way because the moment-generating function does not exist. Salway and Wakefield (2008) suggest that if γ is small (which is likely the case in studies of this type) a three term Taylor approximation

$$\mu_t \approx \exp(\mathbf{z}_t^{\mathrm{T}}\boldsymbol{\alpha})\exp(\gamma\lambda_t^{(1)} + \gamma^2\lambda_t^{(2)}/2 + \gamma^3\lambda_t^{(3)}/6), \tag{3.4}$$

can be used to model ecological bias, where $\lambda_t^{(1)}$ is the first moment and $\lambda_t^{(2)}$ and $\lambda_t^{(3)}$ are the second and third central moments of the log-normal exposure distribution respectively, so here $\lambda_t^{(3)} = \lambda_t^{(2)}/\lambda_t^{(1)}(\lambda_t^{(2)}/[\lambda_t^{(1)}]^2 + 3)$.

3.2.1. *Form of the exposure response function (ERF).* The common simplification that $g(x) = x$ may not be appropriate for air pollution studies, because there must eventually be an upper bound on the effect that air pollution can have on health. An alternative approach is to consider a general function g that satisfies the desirable requirements of: (i) boundedness; (ii) increasing monotonicity; (iii) smoothness (thrice differentiability); and (iv) $g(0) = 0$. Note that these properties are not commonly enforced on CRFs estimated for ambient pollution concentrations using generalised additive models (see for example Daniels et al. (2004)). These assumptions allow $\exp(g(\gamma X_t))$ to be approximated using a three term Taylor expansion of the form

$$\begin{aligned}
\mu_t &\doteq \exp(\mathbf{z}_t^{\mathrm{T}}\boldsymbol{\alpha})\mathbb{E}_{X_t}[\exp\{g(\gamma X_t)\}], \\
&\approx \exp(\mathbf{z}_t^{\mathrm{T}}\boldsymbol{\alpha})\exp(g(\gamma\lambda_t^{(1)}))(1 + \gamma^2 g^{(2)}(\gamma\lambda_t^{(1)})\lambda_t^{(2)} + \gamma^3 g^{(3)}(\gamma\lambda_t^{(1)})\lambda_t^{(3)}), \\
&\approx \exp(\mathbf{z}_t^{\mathrm{T}}\boldsymbol{\alpha})\exp(g(\gamma\lambda_t^{(1)}) + \gamma^2 g^{(2)}(\gamma\lambda_t^{(1)})\lambda_t^{(2)} + \gamma^3 g^{(3)}(\gamma\lambda_t^{(1)})\lambda_t^{(3)}), \qquad (3.5)
\end{aligned}$$

where again $\lambda_t^{(1)}$ is the first moment and $\lambda_t^{(2)}$ and $\lambda_t^{(3)}$ represent the second and third central moments of the log-normal exposure distribution respectively. Ideally the values of the parameters $g^{(r)}$ would be estimated within the MCMC simulation, although in practice it is unlikely that there would be enough information to allow this. Our preliminary analysis suggests the first term $g(\gamma\lambda_t^{(1)})$ can be well approximated by $g(\gamma\lambda_t^{(1)}) = \gamma\lambda_t^{(1)}$, and the lack of information to accurately estimate the derivatives of g leads us to use the values in (3.4); $g^{(2)}(\gamma\lambda_t^{(1)}) = 1/2$ and $g^{(3)}(\gamma\lambda_t^{(1)}) = 1/6$. Note that the effect of the latter two terms of this approximation is likely to be small given the expected small values of γ.

3.2.2. *Health-exposure model.* We assume the daily exposure distributions are log-normal and adopt the ecological bias correction from (3.4), thus extending the models of Dominici and Zeger (2000) and Holloman et al. (2004). The model for relating aggregate mortality counts to a sample of personal pollution exposures at a single lag l is given by

$$
\begin{aligned}
y_t|\{x_{it}\},\beta &\sim \text{Poisson}(\mu_t) \quad \text{for } t = 1,\ldots,n,\\
\ln(\mu_t) &= \lambda_{t-l}^{(1)}\gamma + \lambda_{t-l}^{(2)}\gamma^2/2 + \lambda_{t-l}^{(3)}\gamma^3/6 + \mathbf{z}_t^{\mathrm{T}}\boldsymbol{\alpha},\\
\boldsymbol{\beta} = (\gamma,\boldsymbol{\alpha}) &\sim \text{N}(\boldsymbol{\mu}_\beta,\Sigma_\beta),\\
x_{it}|\lambda_t^{(1)},\lambda_t^{(2)} &\sim \text{Log-Normal}(\lambda_t^{(1)},\lambda_t^{(2)}) \quad \text{for } i = 1,\ldots,k_t,\\
\lambda_t^{(1)}|\sigma^2 &\sim \text{N}(\xi,\sigma^2),\\
\lambda_t^{(2)}|\tau^2 &\sim \text{N}(s^2,\tau^2)_{I[\lambda_t^{(2)}>0]},\\
\sigma^2 &\sim \text{Inverse-Gamma}(0.001,0.001),\\
\tau^2 &\sim \text{Inverse-Gamma}(0.001,0.001),
\end{aligned}
\tag{3.6}
$$

where x_{it} denotes the exposure experienced by individual i on day t. The first two central moments of the daily exposure distribution are treated as unknown and assigned Gaussian priors based on prior knowledge of the mean values. Theoretically different prior means could be assigned to each day (i.e. $\lambda_t^{(1)} \sim \text{N}(\xi_t,\sigma^2)$), but as the information required to sensibly choose values for these is unlikely to be available we use a common underlying mean for all days. The exposure variance $\lambda_t^{(2)}$ is assigned a truncated Gaussian prior because its expected value can be directly specified as a parameter, which would not be the case for standard variance priors such as inverse-gamma.

In such a model, the value of the lag l is typically chosen to be one or two (Dominici et al. (2000)), however the latency over which the health effects manifest themselves is unknown and so the choice of a single lag can be problematic. A possible approach would be to include multiple lags in (3.6) so that the mean function on day t will contain a vector of lagged values, $\mathbf{X}_t = (X_t, X_{t-1},\ldots,X_{t-L})$ with a corresponding vector of effects, $\boldsymbol{\gamma} = (\gamma_0,\ldots,\gamma_L)$. However this mean function is likely to be unsatisfactory due to the high correlation amongst the lagged exposures. This problem of collinearity can be reduced by using distributed lag models (DLM, Zanobetti et al. (2000)). Here, we adapt the DLM approach of Zanobetti et al. (2000), by constraining the coefficients using a Bayesian penalised spline (Lang and Brezger (2004)), with a variance term controlling the amount of smoothing

across lags. Details of the extension of equation (3.6) to incorporate multiple and distributed lag models are provided in the supplementary material available at *http://www.imstat.org/aoas/*. As DLMs allow the effects of multiple lags to be fitted simultaneously, they can be used to assess the possibility of mortality displacement by examining the patterns of effects over short periods of time (Zanobetti et al. (2000)).

4. Case study. In this section we present a case study of data from Greater London and are motivated by three aims: (i) demonstrate the potential of the pCNEM exposure simulator for generating individual exposures for use in air pollution and mortality studies; (ii) investigate the differences between the effects of ambient pollution and personal exposures on mortality; (iii) compare the performance of the log-normal model (3.6) against simpler alternatives that have previously been adopted.

4.1. *Description of the data.* The data used in this study relate to daily observations from the Greater London area during the period 2^{nd} January 1997 until 30^{th} December 1997. The health data comprise daily counts of respiratory mortality for seniors ($\geq$65 years) drawn from the population living within Greater London, and were obtained from the national mortality database. The pollution data relate to concentrations of particulate matter measured as PM_{10}, and the pCNEM exposure simulator uses ambient concentrations measured at eight spatial locations throughout Greater London. The median distance between the monitoring sites was 20km (IQR, 13-25km), and further details of the sites and their locations can be found in Shaddick and Wakefield (2002).

When using the simpler models, average ambient pollution concentrations are calculated as the mean level over the eight monitoring sites. This spatial average is likely to introduce minimal exposure error because PM_{10} concentrations in London during this period exhibit little spatial variation. When fitting the spatio-temporal model suggested in Shaddick and Wakefield (2002), the components of variability attributable to the temporal, spatial and measurement error components account for 80%, 10% and 10% of the total variability respectively. Hence the spatial variation in the ambient measurements is much smaller in comparison to that due to temporal variability. Where there is evidence of strong spatial variability, it may be appropriate to explicitly model the spatial variation in exposure with relation to the health outcome, however in this case the count data were only available in the form of a single (daily) count for the entire area and so a

direct spatial link would not have been possible. Meteorological data (measured at Heathrow airport) were also available for Greater London, including indices of temperature, rainfall, wind speed and sunshine.

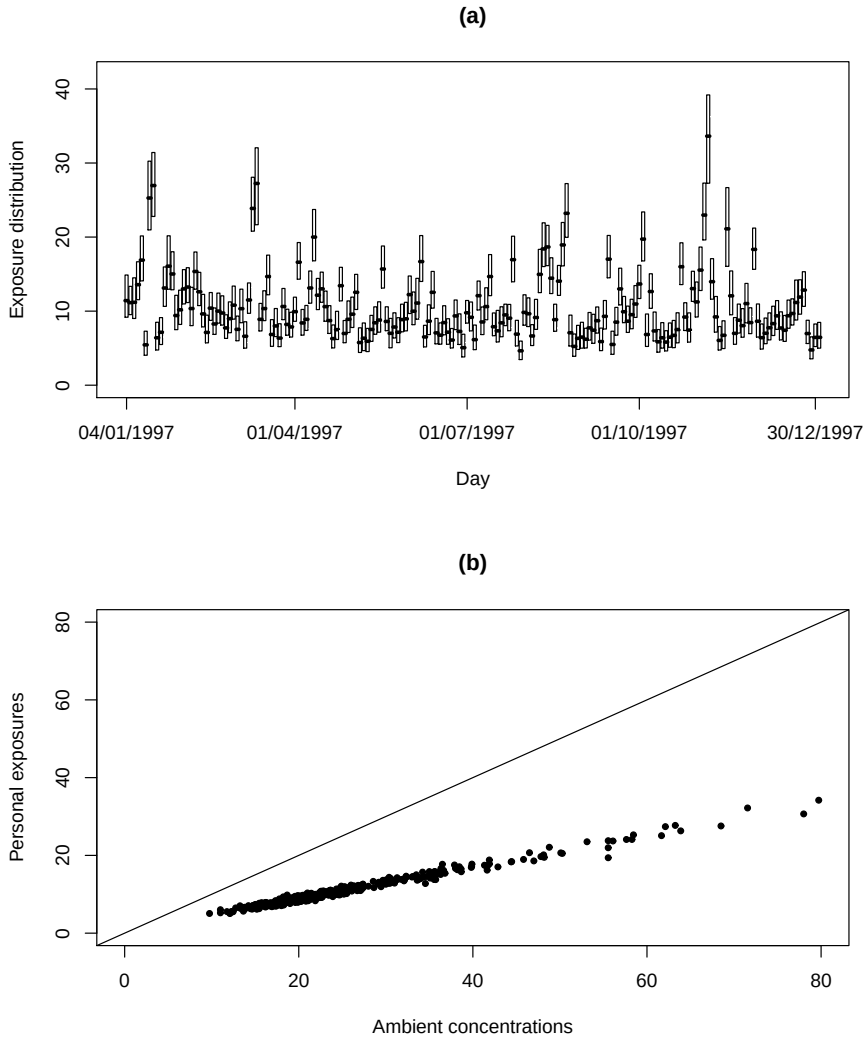
4.2. *Models.* The pCNEM simulator was run with ambient PM_{10} data from the eight monitoring sites described above, together with maximum daily temperatures, further details of which can be found in Zidek et al. (2005). The model generated 100 sets of daily exposures for each of the eight exposure districts (defined as areas around each of the monitoring sites), giving a total of 800 samples for each day. These distributions of estimates (for each day) are shown in panel (a) of Figure 1, while a comparison with ambient concentrations is presented in panel (b). These empirical exposure distributions are then modelled parametrically in the Bayesian hierarchical framework using the following models,

(i) The standard Poisson regression model (equation 2.1) where the daily pollution exposure is fixed at a single value (either the mean of ambient concentrations or the estimated personal exposures).
(ii) The normal exposure model (as in Holloman et al. (2004)) where daily exposures are assumed to follow a normal distribution.
(iii) The log-normal exposure model (as in equation (3.6)) where daily exposures follow a log-normal distribution.

We fitted model (i) to the ambient concentrations and models (i), (ii) and (iii) to the simulated personal exposures. We also investigate possible different effects related to indoor and outdoor sources of pollution exposure, by running the models on these separate components of personal exposures. To assess the sensitivity of our results to our prior assumptions, we apply the log-normal exposure model (3.6) with a range of different priors for (σ^2, τ^2). We adopt an inverse-gamma(ϵ, ϵ) prior with a range of ϵ values and compare this to using a flat prior on the standard deviation scale, as suggested by Gelman (2006). The results were insensitive to these choice of priors.

4.3. *Inference.* Inference is implemented in two stages. In the first, simulated exposures are generated using pCNEM, while in the second these values are used to estimate their association with the mortality counts using the models described in Section 3. The pCNEM exposure simulator generated 800 personal exposures for each of the 363 days in the study, which takes close to an hour to run. In the two stage approach used here this only has to be performed once, rather than within each iteration if a fully Bayesian model was used. In comparison the Bayesian second stage (health model) is relatively computational inexpensive, taking only a few hours to produce

FIG 1. *Panel (a) shows boxplots of the 800 personal exposures by day. For clarity, only every second day is shown and the 'whisker' component is removed. Panel (b) shows the relationship between mean ambient concentrations and mean daily exposure. In both, personal exposures and ambient concentrations of PM_{10} are measured in $\mu g/m^3$.*



a sizeable number of iterations. This was implemented using MCMC simulation from the joint posterior distribution of all parameters conditional on the exposure data generated at stage one, using a mixture of Gibbs sampling steps and block Metropolis-Hastings moves based on random walk proposals. In each case inference about the posterior distribution is based on 20,000 iterations from two Markov chains, initialised from dispersed locations in the sample space (in all cases the starting distributions are an overdispersed version of the prior). Both chains are burnt in for 20,000 iterations, by which point convergence was assessed to have been reached using the diagnostic methods of Gelman et al. (2003).

4.4. *Modelling covariate risk factors.* The covariates ($\mathbf{z}_t^{\mathrm{T}}\boldsymbol{\alpha}$) are used to model any trend, seasonal variation and temporal correlation present in the respiratory mortality series, and are chosen using a fully Bayesian model building process. The mortality data (not shown) exhibit a pronounced yearly cycle, with much less prominent cycles at periods of a half, quarter and eighth of a year. As the most prominent feature is the yearly cycle we began by modelling $\mathbf{y}$ with daily mean temperature, because it also has a yearly cycle. We added temperature to the model as either a linear term or a smooth function, for a number of different lags and moving averages. The smooth function was implemented with variable degrees of freedom using a natural cubic spline, the latter being chosen because its parametric nature makes it less cumbersome to implement in our Bayesian framework than non-parametric alternatives. The fit to the data was compared using the deviance information criterion (DIC, Spiegelalter et al. (2002)) and examining plots of the standardised residuals, and a smooth function of the same days temperature with two degrees of freedom was chosen. Meteorological indices of rainfall, wind speed and sunshine were also included in the model, but they exhibited no relationship with mortality at any lag.

After including temperature in the model the residuals still exhibited cyclical trends, which are typically modelled by functions of calendar time such as smooth functions or pairs of sine and cosine terms. In this study we adopt a smooth function specification, because it is more flexible than sinusoidal terms and has become the method of choice in most recent studies (see for example Daniels et al. (2004)). In common with the temperature covariate we choose the degrees of freedom using the DIC criterion and examining plots of the standardised residuals and selected 11 degrees of freedom. The covariates were therefore

$$\mathbf{z}_t^{\mathrm{T}}\boldsymbol{\alpha} = \alpha_1 + S(t|11, \boldsymbol{\alpha}_2) + S(\text{temperature}_t|2, \boldsymbol{\alpha}_3)$$

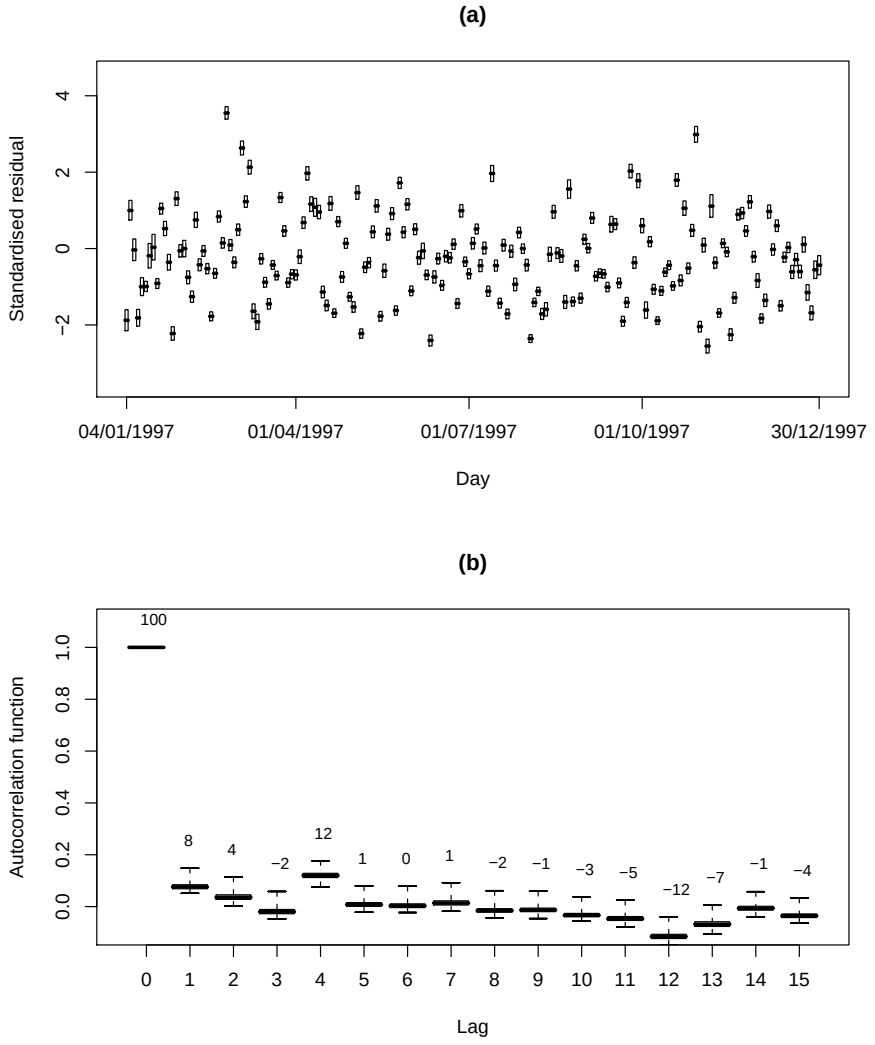
where $S(var|df, \boldsymbol{\alpha}_j)$ denotes a natural cubic spline of the variable *var* with *df* degrees of freedom.

The adequacy of the chosen covariates can be assessed by examining the posterior predictive distributions for the daily residuals (Gelman et al. (2003)) as well as their autocorrelation sequence, both of which are shown in Figure 2. The residual distributions in Figure 2(a) show no clear pattern and the standardised residuals in Figure 2(b) exhibit little or no correlation, suggesting that the covariates are likely to have adequately removed the trends and structure in the mortality data.

4.5. *Relationships between pollution and mortality.* Table 1 gives the estimated relationships between mortality and both personal exposure to and ambient concentrations of PM_{10} for a series of different lags and for two distributed lag models, representing different levels of smoothing. For the separate lags, results are presented on the relative risk scale for an increase in 10 μg/m^3 together with 95% credible intervals. For the DLMs, the total overall risk over a period of eight days is presented. For ambient concentrations, the largest increases in risk were observed with 1 and 2 day lagged ambient concentrations (RR=1.015 (1.01-1.02) and RR=1.02 (1.01-1.04) respectively). For the distributed lag models, DL^1 represents a low level of smoothing over the previous eight days and gives an overall risk of 1.03 (1.00-1.07). The second DL^2 has a higher amount of smoothing and has a correspondingly smaller overall relative risk of 1.02 (1.00-1.05), reflecting the fact that the increased smoothing has essentially averaged the risk at each lag to a single value, resulting in attenuation to the null. Due to the remaining problems of collinearity when using DL^1, the credible intervals are wider than when using DL^2. For DL^1 the highest risks were observed at lags 1 and 2 after which they flattened off towards the null, and in particular did not exhibit a shape indicative of mortality displacement (not shown).

Table 1 shows that for personal exposures the log-normal and fixed exposure models give similar results, estimating higher risks than those observed when using the ambient concentrations. For example, a 10 μg/m^3 increase in lag 2 PM_{10} gives a relative risk of 1.05 (1.01-1.09), compared with 1.02 (1.01-1.04) for ambient concentrations. The distributed lag models also show correspondingly higher values, with the total overall risk being 1.07 (1.00-1.16) and 1.05 (1.01-1.10) when using low and high smoothing respectively.

FIG 2. *Posterior predictive distributions used for model checking. Panel (a) shows the standardised residuals. For clarity only every second day's distribution is shown and the 'whisker' component is omitted. Panel (b) shows the autocorrelation sequence. The numbers denote the median values, multiplied by 100 for ease of presentation.*

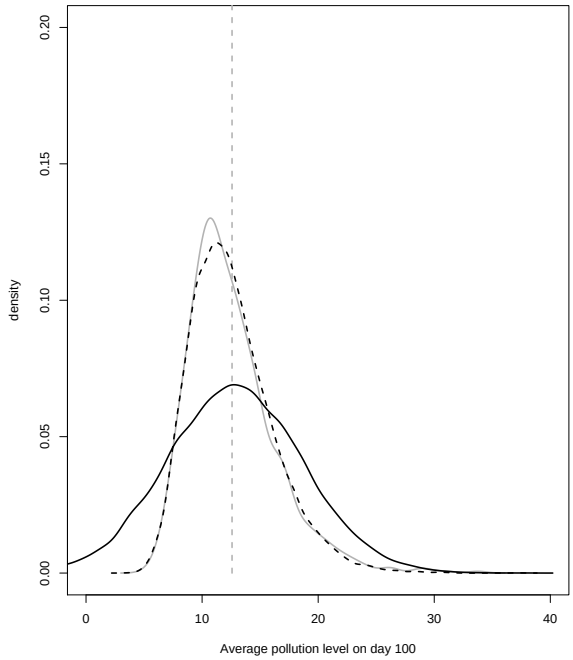


The distributed lag models exhibited the same patterns as with the ambient concentrations, and were again not indicative of mortality displacement.

The normal exposure model estimates a higher relative risk than the other models at all single and distributed lags, with for example a relative risk of 1.07 (1.02-1.12) for lag 2, which is at odds with the corresponding estimates of 1.05. It also does not capture the shape of the exposure distribution across the population, a point which is illustrated in Figure 3. This shows the empirical distribution of the personal exposures for a randomly selected day (11th April 1997), and compares that to the estimated posterior predictive distributions from the proposed models. The empirical distribution is shown by a black dashed line, an illustration of using a single value rather than a distribution is depicted by a dashed grey line, while the solid lines represent posterior predictive estimates from the log-normal (grey) and normal (black) exposure models respectively. The graph shows that the log-normal exposure model produces a distribution that is very close to that of the data, suggesting that the model adequately characterises the daily exposures. In contrast the normal exposure model is a poor approximation to the data, having a larger variance and some posterior predictive probability below zero. Additionally, Holloman et al. (2004) allow only the daily exposure variance to be uncertain, with their model having the general form $\ln(\mu_t) = \lambda_{t-l}\gamma + \mathbf{z}_t^{\mathrm{T}}\boldsymbol{\alpha}, \lambda_t \sim \mathrm{N}(x_t, \sigma^2), \sigma^2 \sim \mathrm{Uniform}(0, 25)$. The posterior estimates of σ^2 are not informative because the Markov chains for this parameter moved quickly between the prior limits and did not converge. This lack of convergence was also observed by the authors and is likely to be caused by their condensing of the simulated daily exposures into a single mean value, so that the model is trying to estimate the variation around that single value.

Table 1 also shows the relative risks separately for the indoor and outdoor sources of pollution, which were estimated by running the pCNEM model with one of the exposure sources turned off. From these separate simulations, the mean daily proportions attributable to indoor and outdoor sources were estimated to be ca. 15% and 85% respectively. For clarity and computational reasons, due mainly to instability in the estimates when using the small proportion of exposures associated with indoor, the association between indoor exposures and mortality was estimated using the standard regression model (ii) with single lags. The table shows that the relative risk and confidence interval (and thus significance) associated with outdoor sources only is very similar to that observed with both sources combined, which is not surprising

FIG 3. *Personal exposure distribution for 11^{th} April 1997. The dashed black line represents the empirical distribution, the dashed grey line is the single fixed exposure, the solid black line assumes a normal exposure, while the solid grey line is the log-normal exposure model.*



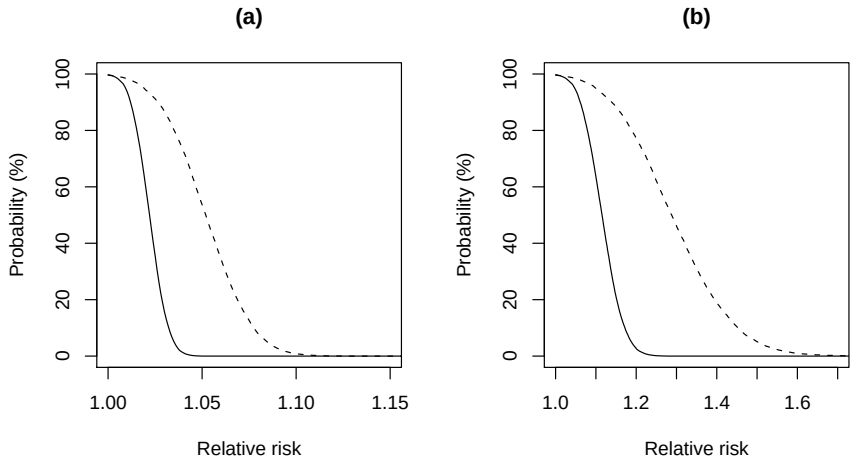
given they make up ca. 85% of total exposure. The risk in relation to indoor sources only is smaller and non-significant, which may be at least partly due to the reasons mentioned above.

TABLE 1

Summary of the posterior relative risks for an increase in 10 $\mu g/m^3$, together with 95% credible intervals and quartiles of the posterior distribution. Results are given for models with lags of 0,1,2 and 3 days and two distributed lag models; DL^1 and DL^2 which respectively have low and high smoothing of the lagged effects over the previous eight days

Data	**Lag**	**2.5%**	**25%**	**50%**	**75%**	**97.5%**
	0	0.993	1.003	1.009	1.014	1.024
Ambient	1	0.999	1.010	1.015	1.020	1.030
model (i)	2	1.007	1.017	1.022	1.027	1.037
	3	0.993	1.003	1.008	1.014	1.024
	DL^1	0.995	1.016	1.027	1.040	1.068
	DL^2	0.990	1.005	1.018	1.031	1.048
	0	0.987	1.013	1.026	1.039	1.064
Personal	1	1.003	1.027	1.040	1.052	1.078
exposures	2	1.013	1.039	1.052	1.065	1.091
model (i)	3	0.980	1.004	1.017	1.030	1.057
	DL^1	0.994	1.046	1.074	1.102	1.159
	DL^2	1.021	1.047	1.059	1.070	1.086
	0	0.993	1.022	1.037	1.053	1.088
Personal	1	1.007	1.036	1.054	1.071	1.105
exposures	2	1.023	1.054	1.070	1.086	1.118
model (ii)	3	0.981	1.010	1.025	1.040	1.075
	DL^1	0.989	1.015	1.104	1.136	1.197
	DL^2	0.993	1.041	1.063	1.098	1.152
	0	0.988	1.014	1.027	1.039	1.065
Personal	1	1.003	1.026	1.039	1.052	1.077
exposure	2	1.013	1.038	1.051	1.065	1.090
model (iii)	3	0.978	1.004	1.018	1.031	1.059
	DL^1	1.001	1.045	1.071	1.101	1.156
	DL^2	1.011	1.027	1.053	1.075	1.090
	0	0.986	1.008	1.021	1.034	1.058
Personal	1	1.000	1.021	1.033	1.046	1.069
exposure	2	1.012	1.035	1.047	1.059	1.083
outdoor only	3	0.981	1.006	1.018	1.029	1.053
	0	0.417	0.828	1.187	1.716	3.487
Personal	1	0.211	0.415	0.597	0.839	1.649
exposure	2	0.371	0.729	1.033	1.474	2.924
indoor only	3	0.349	0.664	0.910	1.256	2.346

FIG 4. *Probabilities that the relative risk exceeds certain values. The solid line refers to the model using ambient concentrations, while the dotted line relates to modelled personal exposures. Panels (a) and (b) show the results for 10 $\mu g/m^3$ and 50 $\mu g/m^3$ changes in PM_{10} respectively.*



4.6. *The relationship between ambient concentrations and personal exposures.* In this paper the implementation of the pCNEM exposure simulator allows us to relate personal exposures to mortality, in addition to the standard use of ambient concentrations. For clarity, in the following example, the results from models using a single lag of 2 days are discussed. Table 1 shows that the median relative risk from exposure to ambient concentrations is 1.02, less than half that obtained when personal exposures are used. The difference in the effects of personal exposures and ambient concentrations can be seen in Figure 4, which shows $P(RR > c)$ for various values of c, where panel (a) relates to a relative risk for an increase in 10 $\mu g/m^3$ where as for panel (b) it is 50. The plots show clearly that $P(RR > c)$ is bigger when using personal exposures than ambient concentrations, except for the case when c=1 (both probabilities are close to one) or when c is very large (both probabilities are close to 0). For example from panel (a) $P(RR > 1.02) = 60.0\%$ using ambient concentrations, compared with $P(RR > 1.02) = 94.3\%$ for personal exposures. This result is not surprising as the population spend a large proportion of time indoors (and away from the major outdoor sources of pollution), meaning that ambient concentrations are likely to be larger than personal exposures leading to different relative risks with mortality, a point which is now discussed in more detail.

The daily averages (means) of ambient concentrations and personal exposures from Greater London appear to be linearly related (see Figure 1 panel (b)), with the latter being smaller by a factor of about 2.4 in this example. The same set of mortality data are used to model both pollution measures, meaning that the combined pollution-effect component of the regression model, $\lambda_{t-l}\gamma$, should remain constant regardless of the exposure size. This relationship between the γ regression coefficients for the ambient and personal pollution exposures holds more generally with linearly related covariates. Let (x_t^A, x_t^P) denote ambient and personal exposures respectively, and consider the log linear models

$$\mathbb{E}[y_t] = \exp(x_{t-l}^A\gamma + \mathbf{z}_t^{\mathrm{T}}\boldsymbol{\alpha}) \tag{4.1}$$

$$\mathbb{E}[y_t] = \exp(x_{t-l}^P\gamma^* + \mathbf{z}_t^{\mathrm{T}}\boldsymbol{\alpha}^*) \tag{4.2}$$

used here where (γ, γ^*) are the parameters relating mortality to ambient concentrations and personal exposures respectively. Assuming the two measures of pollution are linearly related, that is $x_t^P = \theta + \phi x_t^A$, the model with personal exposures (equation 4.2) can be re-written as

$$\mathbb{E}[y_t] = \exp(x_{t-l}^A\phi\gamma^* + \theta\gamma^* + \mathbf{z}_t^{\mathrm{T}}\boldsymbol{\alpha}^*),$$

an alternative representation of the ambient model (equation 4.1). Equating the coefficients of the ambient pollution level x_t^A, we see that (γ, γ^*) are related as $\gamma = \phi\gamma^*$. Therefore if the ambient concentrations and personal exposures are highly correlated, then the estimated regression coefficient of the former can be determined from the latter (and vice versa) just by calculating their linear regression equation. For the Greater London data analysed here $x_t^P \approx 0.83 + 0.40x_t^A$, meaning that $\gamma \approx 0.4\gamma^*$, which can be verified by comparing the posterior medians from Table 1. Similar relationships are also observed by Dominici and Zeger (2000), who estimate linear regressions of mean personal exposure against mean ambient concentrations for PM_{10} from five studies. They report estimates of ϕ ranging from 0.33 to 0.72, with a pooled estimate of 0.53. Recently, McBride et al. (2007) used a Bayesian hierarchical model to characterise the relationship between personal exposures and ambient concentrations of $PM_{2.5}$ for a small group of seniors in Baltimore. They also observed that using ambient concentrations would result in overestimates of personal exposure, with a mean attenuation of 0.6 (albeit with a large range). These estimates are in line with the value of 0.4 observed here, suggesting that the simulated exposures generated by the pCNEM simulator are likely to be of the correct size relative to ambient concentrations.

5. Discussion. This paper presents a two stage approach to constructing exposure response functions (ERFs), relating to the health effects of an environmental hazard monitored over time and space. The first component uses a computer model involving ambient pollution and temperature inputs, to simulate the exposure to that hazard experienced by individuals in an urban area. The model incorporates the mechanisms that determine the level of such exposures, such as the activities of individuals in different locations which will lead to differing exposures. The outputs from the model take the form of a set of exposures, experienced by a random sample of individuals from the population of interest for each day of the study. These daily samples can be approximated by a parametric distribution, so that the predictive exposure distribution of a randomly selected individual can be determined. The second component incorporates these distributions into a hierarchical Bayesian framework, that jointly models the relationship between the daily exposure distributions (incorporating the within-day between individual variation) and health outcomes, whilst modelling potential confounders using splines.

The approach was applied to a study of the association between particulate pollution (PM_{10}) and respiratory mortality in seniors (in London, 1997). Models using ambient concentrations and (estimated) personal exposures were compared, with the latter being represented by a single measure of pollution for each day, as well as modelling the inherent variability using both log-normal and Gaussian distributions. The use of a log-normal distribution to represent daily variability in personal exposures is more satisfactory than the Gaussian alternative, both in a statistical sense and in term of the physical properties of the processes that might determine concentrations. In this application the terms intended to allow for ecological bias proved to be negligible, meaning the health effects model was essentially log-linear and there was little difference in incorporating an appropriate parametric distribution for daily exposures and using a single summary measure. As such, in this case a simpler model could have been used, although this could not have been known *a priori* and may not be true for other environmental hazards. Using the computer simulation model showed that personal exposures to PM_{10} are likely to be significantly lower (ca. 40%) than measured ambient concentrations used in regulatory standards. This implies that their relative risk (of personal exposures) is higher than the ambient analysis would suggest (ca. 2.5 times). The relative risk associated with (lag two) ambient concentrations to PM_{10} was RR=1.02 (1.01-1.04), with the corresponding risk associated with personal exposures being RR=1.05 (1.01-1.09). Similar

increases between risk estimates when using (estimated) personal exposures are observed for all lags.

This increase in observed risk is in a large part due to the fact that the population spend a large amount of their time indoors, meaning that personal exposures (which come from indoor sources such as cooking with gas, as well as a proportion of outdoor sources determined by factors such as the air exchange rate) are likely to be lower than ambient concentrations (Zidek et al. (2007)). In terms of public policy it is ambient concentrations that may be controlled rather than personal exposures per se, and so the risks associated with ambient concentrations are of interest in their own right, in addition to the risk associated with personal exposures explored here. Of course, one aim of policies that reduce ambient concentrations would be a reduction in exposures experienced by individuals. One potentially very useful facility which pCNEM offers is the ability to assess the effect of such reductions in ambient concentrations on personal exposures (see Zidek et al. (2005) for an example). Ambient source exposures are derived from the outdoor environment and are thus shared amongst the population, whereas non-ambient exposures come from individual environments that are not shared (Sheppard (2005)). As such, careful interpretation of the meaning of the relative risk is required when comparing studies using personal exposures and ambient exposures (Sheppard et al. (2005)). The traditional time series approach relies on the assumption that it is the (relatively) short-term temporal changes in ambient concentrations that determine the relative risk coefficients (RRCs), and not the spatial variation in exposure to indoor sources captured by the ERF. As such, the ERF's RRCs will be (largely) determined by the ambient concentrations (Lianne Sheppard, personal communication with the third author, and also observed for the Greater London data analysed here, see Table 1). In fact, the RRCs in the CRF and ERF differ only in that the latter compensates for the lower level of predicted exposures compared with the ambient concentrations (observed for the simulated exposures generated here, the five small scale studies documented by Dominici and Zeger (2000) and the study of McBride et al. (2007)). For example if exposures were 50% of ambient concentrations, the RRC for the ERF will have to be twice as large (since the disease effect function is roughly linear) to predict the same observed numbers of health outcomes.

This disattenuation of the RRC could be done entirely with the help of statistical models (Sheppard et al. (2005)). However there will be difficulties in estimating the necessary parameters required for an entirely statistical

approach, i.e. the relationship between ambient concentrations and personal exposures for a specific sub-population, such as seniors. The attempt to incorporate the mechanisms of how individuals are exposed rather than adopting a purely statistical approach also helps provide a more scientific basis for setting standards and analysing health effects even when in some cases the results may turn out to be similar. The use of the computer simulation model to estimate individual exposures, and thus the ERF, therefore appears to have great potential in cases such as this, especially where the (potentially suspectable) sub-group being studied might not be expected to be well represented by using (overall) ambient concentrations of pollution.

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